Bioactive Carbohydrates and Dietary Fibre 17 (2019) 100170

Contents lists available at ScienceDirect

Bioactive Carbohydrates and Dietary Fibre

journal homepage: www.elsevier.com/locate/bcdf

Dietary fibers and their fermented short-chain fatty acids in prevention of human diseases

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ARTICLE INFO

Keywords:
Fatty acids
Butyrate
Cancer
Diet

ABSTRACT

Many studies show that daily consumption of high-fiber diet reduces the risk of developing kidney stones, inflammatory disease, colon cancer and other malignancies, obesity, type II diabetes, and cardiovascular disease. Dietary fibers are non-digestible polysaccharides that are composed of complex carbohydrates. Based on their relative solubility in water, dietary fibers can be divided into insoluble and soluble forms. Soluble fibers absorb water to form a gel in the intestine. Soluble fibers with the exception of *Psyllium* are more readily fermentable by the colon probiotic bacteria than insoluble fibers. An important property of insoluble fibers is the ability to bind with carcinogens, mutagens, and other toxic chemicals that are formed during digestion of food, and eliminate them through the feces. Soluble fibers can be degraded to short-chain fatty acids, such as butyrate, propionate, and acetate by fermentation. This review discusses mechanisms of action of fibers and their beneficial effects on the GI tract as well as on other organs. Among short-chain fatty acids, butyrate has been most extensively studied and the effects of sodium butyrate on cell culture and animal models are discussed in order to emphasize its potential value in prevention of certain diseases.

1. Introduction

There is much evidence from epidemiologic, and intervention studies that show health benefits of daily consumption of high-fiber diet fibers in humans. These health benefits include reducing the risk of developing kidney stones (Sorensen et al., 2014), inflammatory disease (Andoh, Tsujikawa, & Fujiyama, 2003), colon cancer and other cancers (Wong, DE Souza, Kendall, Emam, & Jenkins, 2006), obesity, type II diabetes, and cardiovascular disease (Lattimer & Haub, 2010). However, the types of fiber involved in these protective processes are not fully understood. The Institute of Medicine Food and Nutrition has proposed a distinction between two types of fibers natural dietary fibers and added fibers. However, this distinction is vague and it is difficult to evaluate their respective health benefits. The only demonstrable difference between the two is the presence of lignin in the dietary fiber but not in the added fiber. Dietary fibers are defined as non-digestible polysaccharides largely composed of complex carbohydrates. Based on their relative solubility in water, dietary fibers can be divided into insoluble and soluble forms. Soluble fibers absorb water to form a gel in the intestine, and with the exception of *Psyllium* are more readily fermentable by the colon bacteria than insoluble fibers. Most dietary fibers commonly found in food contain both insoluble and soluble components and their proportion may differ depending upon the diet. For example, fresh fruits and vegetables contain more soluble than insoluble fibers, whereas cereals contain more insoluble than soluble fibers (Otles & Ozgoz, 2014). Dietary fibers include arabinoxylan, inulin, pectin, bran, cellulose, hemi cellulose, beta-glucan, and resistant starch (Lattimer & Haub, 2010). Soluble fibers contain pectins, beta-glycan, gums, guar fibers, inulin, and resistant starch, whereas insoluble fibers contain lignin, cellulose and hemicellulose (Fig. 1).

An important property of insoluble fibers is their ability to bind with carcinogens, mutagens, and other toxic chemicals formed during digestion of food, allowing their subsequent removal through the feces, whereas soluble fibers are able to produce short-chain fatty acids, such as butyrate, propionate, and acetate by fermentation in the colon. The amounts of short-chain fatty acids formed during this fermentation depend upon the exact site of fermentation, levels of fibers in the diet, gut transition time, and composition of the colonic microbiome.

This review discusses mechanisms of differential actions of soluble and insoluble fibers in producing beneficial effects on the GI tract as well as other organs. Among short-chain fatty acids, butyrate has been most extensively investigated and its effects in cell culture and in animal models are discussed in more detail in order to illustrate its potential value in prevention of certain diseases.

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https://doi.org/10.1016/j.bcdf.2018.09.001
Received 21 January 2018; Received in revised form 17 July 2018; Accepted 26 September 2018

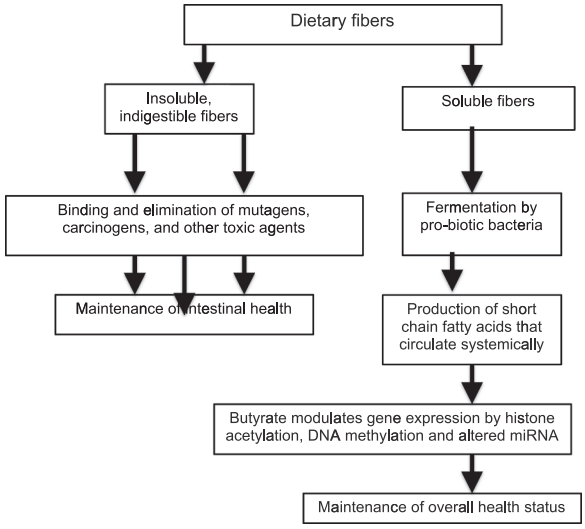

Fig. 1. Dietary fibers and their fermentation products affecting health.

2. Mechanisms of action of dietary fibers

The mechanisms of action of fiber depend upon the type of fiber. The ability of insoluble fibers to bind with several toxic chemicals including carcinogens and mutagens allows these harmful materials to be eliminated through the feces. The main beneficial feature of soluble fibers is their ability to produce large amounts of short-chain fatty acids by fermentation with the help of probiotic bacteria in the lower colon (Ferguson & Harris, 1996). These short-chain fatty acids include butyrate, acetate, and propionate; however, butyrate is probably the major factor in maintaining colonic homeostasis and in countering various diseases (Galvez, Rodriguez-Cabezas, & Zarzuelo, 2005). Butyrate is a 4-carbon fatty acid that is rapidly absorbed from the gut. Exposure to sodium butyrate can lead to modification of histones by acetylation, phosphorylation of other proteins, and methylation of DNA thereby modifying genomic expression. Propionate after absorption from the intestine inhibits cholesterol synthesis and is primarily accumulated in the liver, whereas acetate after absorption into the blood stream increases the synthesis of cholesterol (Wong et al., 2006).

The potential value of butyrate in prevention of certain diseases is suggested by studies performed in cultured cells and animals. Isolated cells have been directly exposed to varying concentrations (1–5 mM) (Giuliano et al., 1999; Stoilov et al., 2000) whereas animals were often injected intraperitoneally with doses 50–1200 mg/kg of body weight (Gagliano, Delgado-Morales, Sanz-Garcia, & Armario, 2014; Kanika, Khan, & Jena, 2015; Liu et al., 2015; Sun, Zhang, Hong, Zhang, & Kong, 2013). These high levels may not be not relevant for humans.

3. Butyrate and cancer

The ability of butyrate to retard cancer initiation was accidently discovered while investigating the effect of dibutyryl cyclic AMP on neuroblastoma cells in which sodium butyrate was used as a control. While dibutyryl cyclic AMP induced terminal differentiation in neuroblastoma cells, sodium butyrate alone caused growth inhibition in these tumor cells (Prasad & Hsie, 1971). In addition, sodium butyrate enhanced the cell killing effects of X-radiation, chemotherapeutic agents, and cyclic AMP stimulating agents (Prasad, 1979). The first review on diverse biological action of butyric acid was published in 1980. Since then hundreds of articles have been written on growth inhibitory effects of butyric acid on various cancer cells.

3.1. Acetylation of histones, phosphorylation of proteins, and methylation of DNA by sodium butyrate

Sodium butyrate inhibited histone deacetylase leading to hyperacetylation of these basic proteins and loosening of their attachment to DNA. This allowed increased transcription of genes and caused apoptosis in cancer cells (Gospodinov, Popova, Vassileva, & Anachkova, 2012; Luhrs et al., 2002; Smith, Yokoyama, & German, 1998). In cultured fibroblasts, sodium butyrate treatment increased methylation of DNA (Boffa, Mariani, & Parker, 1994). Sodium butyrate regulates methylation of DNA differently in normal cells and transformed cells induced by Simian viruses-40 and gamma-irradiation (de Haan, Gevers, & Parker, 1986). Treatment with sodium butyrate enhanced phosphorylation of retinoblastoma pRb protein and caused apoptosis in human vestibular Schwannoma cells in culture (Mitra, Devi, Gope, Subbakrishna, & Gope, 2012). Sodium butyrate treatment enhanced phosphorylation of tyrosine in erythroleukemic cells. It also caused hyperphosphorylation of tyrosine in several proteins and led to activation of MAP kinase (ERK-1) leading to apoptosis in cancer cells (Rivero & Adunyah, 1996).

3.2. Regulation of microRNAs by sodium butyrate in cancer cells

MicroRNAs (miRs) are evolutionarily conserved small non-coding single-stranded RNAs of approximately 22 nucleotides in length and are present in all living organisms (Lee, Feinbaum, & Ambros, 1993; Londin et al., 2015; Macfarlane & Murphy, 2010; Wightman, Ha, & Ruvkun, 1993). The synthesis of miRs involves multiple biochemical steps. Most miRs are transcribed by RNA polymerase II (Pol II), while some are transcribed by RNA polymerase III (Pol III) from the non-coding region of the DNA to generate primary miRs (pri-miRs). Pri-miRs then undergo a nuclear cleavage by ribonuclease III Drosa in the nucleus leading to generation of precursor-miRs (pre-miRs) that move to the cytoplasm. Here they are further cleaved by ribonuclease III Dicer to form mature single-stranded miRs with the help of another protein argonaute (Ago) (Denli, Tops, Plasterk, Ketting, & Hannon, 2004; Hutvagner et al., 2001; Lee et al., 2003; Macfarlane & Murphy, 2010). Each miR is able to bind to its complimentary sequence in the 3′-untranslated region (3′-UTR) of a specific mRNA, leading to degradation of the mRNA transcript, and this prevents translation of the message into the corresponding protein. By this means, miRs can prevent the translation of pro-apoptotic or anti-apoptotic proteins from their respective mRNAs, depending upon whether they receive injurious or protective signals.

Tissues containing sporadic human colon cancer cells have several-fold elevated levels of miR-92a compared to adjacent normal colon tissue. However, treatment of human colon cancer cells with butyrate attenuated the levels of pri-miR-17–92a, a precursor of mir-92a, and miR-92a, and its target protein c-myc (Macfarlane & Murphy, 2010). Reduction of levels of miR-92a led to decreased levels of c-myc. Overexpression of miR-92a reversed the inhibitory effects of butyrate on colon cancer cells. Sodium butyrate treatment also enhanced the expression of miR-203 and this prevented the translation of the NEDD9 gene (which is found in neural precursor cells and down-regulated during development, but highly expressed in some tumor types) induced apoptosis, growth inhibition, and prevented colony formation and cell invasion by tumor cells (Han, Sun, Wu, Zheng, & Zhao, 2016). Treatment of breast cancer cells with sodium butyrate up-regulated the expression of miR-31 which led to suppression of the levels of polycomb group (PcG) protein BM11 and induction of cellular senescence (Cho, Dimri, & Dimri, 2015). Thus, by up- or down-regulation of specific miRs, butyrate can effectively block colonic tumor progression.

4. Sodium butyrate and inflammatory disorders

Sodium butyrate suppressed colonic inflammation by inducing T cell apoptosis and inhibited interferon-gamma levels in cultured colonic

mucosal cells derived from patients with ulcerative colitis (Zimmerman et al., 2012). Butyrate treatment induced differentiation of colonic regulatory T (Treg) cells that play an important role in suppression of inflammatory responses (Furusawa et al., 2013). In the rat model of colitis, administration of sodium butyrate increased the number of Treg cells in the peripheral blood and enhanced the levels of the anti-inflammatory cytokine IL-10 in plasma. Sodium butyrate also suppressed the levels of pro-inflammatory IL-17 in both plasma and colonic mucosa leading to elimination of the inflammatory lesion found in colitis (Zhang, Zhou et al., 2016). Butyrate also inhibited pro-inflammatory cytokine-induced activation of NF-kappaB (Andoh et al., 2003). A low-fiber diet aggravated the inflammatory response in an ovalbumin-induced allergic reaction in mice, whereas a high-fiber diet significantly reduced the allergic symptoms (Zhang Shi et al., 2016).

5. Butyrate and neurodegenerative diseases

In addition to acting as an inhibitor of histone deacetylase, butyrate also functions as a ligand for a subset of G-protein-coupled receptors (Bourassa, Alim, Bultman, & Ratan, 2016). Using pathways mediated by butyrate, fiber metabolism in the gut could alter gene expression in other organs including the brain. The reported anti-depression effect of sodium butyrate may be mediated by altering the expression of several genes that include upregulation of transthyretin (Ttr) and down-regulation of the serotonin 2A receptor (Htr2A). In a rat model of depression, treatment with sodium butyrate causes hypermethylation of DNA that is mediated by demethylation-facilitating enzymes such as ten-eleven translocation methylcytosine dioxygenase 1 (TET1) (Wei, Melas, Wegener, Mathe, & Lavebratt, 2014).

Sodium butyrate treatment attenuated cerebral ischemic injury in mice by normalizing levels of lipid peroxidation, superoxide dismutase (SOD), and IL-1β, IL-alpha, IL-8. Such treatment also inhibited apoptosis most likely by decreasing levels of caspase-3 and Bax (Sun et al., 2015).

Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant neurodegenerative disease caused by polyglutamine-expanded ataxin-3. In transgenic mice expressing disease-causing ataxin-3-Q79, treatment with sodium butyrate reversed ataxin-3-Q79-induced histone hypoacetylation and transcriptional inhibition and reduced the symptoms of the disease, increasing overall survival rate (Chou, Chen, Yeh, Weng, & Wang, 2011). Sodium butyrate reduced glial fibrillary acidic protein (GFAP) content in both primary human astrocytes and astrocytoma cells, and stimulated the reorganization of the intermediate filament network (Kanski et al., 2014). This observation is important because the dysregulation of GFAP gene expression can lead to the aggregation of GFAP, a hallmark of astroglial inflammation, found in human leucodystrophy (Alexander disease).

Dentatorubral-pallidoluysian atrophy (DRPLA) is a progressive neurodegenerative disease caused by the expansion of the terminal polyglutamine of the atrophin-1 protein. In transgenic mice (Atro-118Q) expressing the mutant human atrophin-1 gene, treatment with sodium butyrate reversed hypoacetylation, improved motor function, and extended the lifespan (Ying et al., 2006). Over-expression of alpha synuclein gene or mutation in alpha-synuclein gene is an important factor in the pathogenesis of Parkinson's disease. Treatment with sodium butyrate of dopaminergic neurons expressing increased levels of both the wild-type alpha-synuclein gene or the mutated alpha-synuclein gene found in familial Parkinson's disease, and prevented DNA damage by rescuing DNA repair enzymes, thereby protecting neurons (Paiva et al., 2017).

In the mouse model of spinal muscular dystrophy (SMA), associated with a deficit of spinal motor neuron protein (SMP) sodium butyrate treatment increased the levels of SMP in motor neurons of the spinal cord and improved the clinical symptoms of SMA (Chang et al., 2001).

6. Sodium butyrate and diabetes

Because of its ability to inhibit histone deacetylase, butyrate has been suggested as a treatment for diabetes (Khan & Jena, 2015). In support of this proposal, sodium butyrate has been found to enhance beta-cell development, proliferation, differentiation, and function and reduce diabetic-related microvascular complications (Christensen et al., 2011). Sodium butyrate application enhanced renal function and prevented fibrosis, apoptosis and DNA damage in the kidney of juvenile diabetic rats (Khan & Jena G., 2014). Butyrate also decreased plasma glucose, HBA1c, and improved plasma insulin levels in these rats (Khan & Jena G.B, 2014). In addition, sodium butyrate treatment reduced plasma glucose, HbA1c, insulin resistance, lipid abnormality, and glucogenesis in a manner comparable to the commonly used drug metformin (Khan & Jena, 2016). Sodium butyrate markedly reduced diabetes-induced loss of learning ability, memory, and endothelial function in streptozotocin treated diabetic rats with vascular dementia (Sharma & Singh, 2011). The development of anti-islet-cell autoimmunity generally precedes diabetes type1. Dietary fiber-generated butyric acid can be protective against type 1 diabetes by causing inhibition of the production of anti-islet-cell autoantibodies (Endesfelder et al., 2016). In a rat insulinoma cell line (RINm5F), treatment with sodium butyrate induced differentiation, increased cellular insulin levels and insulin production, and expression of insulin mRNAs (Swarovsky, Eissele, Eisenacher, Trautmann, & Arnold, 1994). Propionate, another small fatty acid that is generated during fermentation of soluble fiber, did not produce any parallel beneficial effects in streptozotocin-induced diabetic rats (Cameron-Smith, Collier, & O'dea, 1994).

7. Sodium butyrate and cardiovascular disease

Treatment of ApoE knockout mice with sodium butyrate slowed the progression of atherosclerosis in the aorta by reducing adhesion and migration of macrophages and increasing the stability of the plaque (Aguilar et al., 2014). It also reduced oxidative and inflammatory events at the lesion site by decreasing NADPH oxidase and decreasing NFκB activation (Aguilar et al., 2016).

8. Propionate and acetate

Propionate and acetate are other short-chain fatty acids that are generated during fermentation of dietary fibers in the colon. Propionate has been implicated in lowering lipids, serum cholesterol levels, and reducing the incidence of cancer (Hosseini, Grootaert, Verstraete, & Van De Wiele, 2011). Propionate administration increased the release of peptide YY (PYY) and glucan like peptide-1 (GLP-1) from cultured human colonic cells, and in a randomized, controlled 24-week study involving 60 overweight adults, significantly reduced weight gain, intra-abdominal adipose tissue distribution, hepatocellular lipid content. In addition, there was evidence of improved insulin sensitivity in this population (Chambers et al., 2015). Colonic production of propionate may play an important role in reducing reward-based eating behavior via striatal pathways, independent of changes in the levels of PYY and GLP-1 (Byrne et al., 2016). However, the half life of propionate in humans is less than 3 h, which may limit clinical utility (Walter, Thompson, Leonard, Heatherington, & Bartlett, 1989).

Sodium acetate induced apoptosis in colorectal cancer cells (Oliveira et al., 2015). Like propionate, sodium acetate administration enhanced the levels of PYY and GLP-1, and it also suppressed TNF-alpha in hyperinsulinemic women (Freeland & Wolever, 2010). Also parallel to propionate, sodium acetate reduced appetite (Frost et al., 2014). It has been suggested that sodium acetate could replace sodium bicarbonate on an equimolar basis for use in medical toxicology (Neavyn, Boyer, Bird, & Babu, 2013). The plasma half-life of acetate is about 2 min in sheep (Al-Mamun, Goto, Chiba, & Sano, 2009).

9. The potential value and limitations of butyrate in disease prevention

Production of butyrate during fermentation of primarily soluble fibers is a continual process in the lower colon, and thus butyrate could play a role in the prevention of a range of human illnesses, such as cancer, diabetes, cardiovascular diseases, and inflammatory disorders. Furthermore, butyrate may also be useful as a tool both to investigate the molecular mechanisms underlying these diseases and in the development of related pharmacological therapeutic analogs.

The therapeutic value of exogenously administered sodium butyrate is limited by its very short plasma half-life. In mice and rabbits, half -life of sodium butyrate in the blood was less than 5 min. In humans, the elimination curve of sodium butyrate has two components: a very rapid elimination slope yields a half-life of 0.5 min, whereas a slower elimination slope provides a half-life of 13.7 min (Daniel et al., 1989). However, the biological half-life of short chain fatty acids may be extended by their administration as esters such as the inulin ester (Polyviou et al., 2016). Although the therapeutic doses of sodium butyrate can be achieved by slow i.v infusion, its extreme unpleasant smell makes this fatty acid unlikely to be used in any disease treatment.

10. Conclusions and summary

In 2015, the Academy of Nutrition and Dietetics recommended a daily consumption of total fiber of 14 g per 1000 kcal or 25 g for adult women and 38 g for adult men. This was based on reports demonstrating protection by dietary fiber against coronary heart disease (Dahl & Stewart, 2015). This recommendation is also likely to be relevant for protection against other diseases. The mean daily intake of dietary fiber by the US population is about 17 g/day (Dahl & Stewart, 2015). The proportions of soluble and insoluble fibers that can produce optimal health benefits in human remain to be determined.

Dietary fibers can reduce the incidence of colorectal cancer as well as improving overall intestinal health. The ability of insoluble fibers to bind with mutagens and carcinogens, effecting their elimination through the feces, together with the production of beneficial short-chain fatty acids by fermentation of soluble fibers, can have a significant overall health impact. These combined properties are likely lead to reduce the incidence of colorectal cancer and other malignancies as well as non-neoplastic diseases, such as diabetes, cardiovascular disease and immune disorders. Despite their short half-life in the plasma, fiber-generated short-chain fatty acids, as they are generated for prolonged periods during digestion, are likely to be beneficial in reducing the incidence of specific diseases.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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